## Antibody Conditioning Enables MHC-Mismatched Hematopoietic Stem Cell Transplants and Organ Graft Tolerance.

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**Public Summary:**
Transplantation of blood forming stem cells can correct many blood and immune disorders by replacing a diseased blood system with a healthy one. However, this procedure requires depleting a patient's existing blood forming system and immune cells using toxic and non-specific chemotherapy, radiation, or both. This study shows in mice that proteins, called antibodies can accomplish this goal with reduced toxicity by specifically targeting cells within the blood/immune systems. Recipients were pre-treated with six antibodies targeting the specific blood and immune system molecules present on macrophages, lymphocytes and blood stem cells, followed by donor blood stem cell transplantation. Stable donor grafts regenerated blood formation in recipients even when transplanted across major immunologic barriers. This approach allowed co-transplantation of blood stem cells with heart tissue from the same donor and permitted survival of the donor heart without immune suppression. Recipients that received grafts from very immunologically different donors still developed normal immune responses, demonstrating preservation of functional immunity after this procedure. These findings suggest approaches for transplanting immunologically mismatched blood stem cells and solid organs with limited toxicity.

**Scientific Abstract:**
Hematopoietic cell transplantation can correct hematological and immunological disorders by replacing a diseased blood system with a healthy one, but this currently requires depleting a patient's existing hematopoietic system with toxic and non-specific chemotherapy, radiation, or both. Here we report an antibody-based conditioning protocol with reduced toxicity and enhanced specificity for robust hematopoietic stem cell (HSC) transplantation and engraftment in recipient mice. Host pre-treatment with six monoclonal antibodies targeting CD47, T cells, NK cells, and HSCs followed by donor HSC transplantation enabled stable hematopoietic system reconstitution in recipients with mismatches at half (haploidentical) or all major histocompatibility complex (MHC) genes. This approach allowed tolerance to heart tissue from HSC donor strains in haploidentical recipients, showing potential applications for solid organ transplantation without immune suppression. Fully mismatched chimeric mice developed antibody responses to nominal antigens, showing preserved functional immunity. These findings suggest approaches for transplanting immunologically mismatched HSCs and solid organs with limited toxicity.